1. INTRODUCTION

1.1 Aim of the application

Lepirudin, a recombinant hirudin derived from yeast cells, was approved in the United States in 1998 for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications. Approval has also been granted for lepirudin in this indication in Canada, the European Union (15 countries) and 15 other countries. Post-marketing experience with lepirudin is available from an extensive 2-year drug monitoring program. The program involved a total of 1,329 patients in Europe and confirmed the positive results obtained with lepirudin in the clinical trial program for HIT.

In the current efficacy supplement, the following indication for REFLUDAN® [lepirudin (rDNA) for injection] is being sought:

> REFLUDAN is indicated for anticoagulation in adult patients with acute coronary syndromes (unstable angina or acute myocardial infarction without ST elevation). In this setting, REFLUDAN has been shown to decrease the rate of cardiovascular death or new myocardial infarction (combined double endpoint), as well as the rate of cardiovascular death, new myocardial infarction or refractory angina (combined triple endpoint).

The lepirudin dosage proposed for the new indication (0.4 mg/kg bolus + 0.15 mg/kg/hour infusion) is the same as that used in the approved HIT indication.

1.2 Epidemiologic background

Acute coronary syndromes (ACS), i.e. unstable angina and acute myocardial infarction (MI) without persistent ST elevation, constitute a significant public health problem. They result in about 1 million hospitalizations per year in the United States alone, and are now a more common reason for hospitalization than acute MI with ST elevation [1]. Assuming a similar hospitalization rate in Europe, the overall number of hospitalizations for ACS in North America and Europe is estimated to be at least 2 million per year.

1.3 Pathophysiology of ACS

ACS are caused by rupture of an atherosclerotic plaque, which leads to activation of blood coagulation and platelet activation, which in turn results in complete or partial thrombotic occlusion of the culprit coronary artery [2, 3, 4, 5]. The thrombotic response and clinical presentation are thought to be influenced by the extent of the arterial injury. Deep arterial injury with more complete and persistent occlusion is more likely to lead to acute MI, whereas superficial arterial injury with partial and intermittent occlusion presents as unstable angina [2]. There is a pathophysiologic continuum between these two manifestations of acute myocardial ischemia, often with considerable overlap in clinical presentation and treatment.

Thrombin plays a key role in the pathogenesis of ACS. The formation of thrombin is triggered by tissue factor exposed at sites of vascular injury. Once formed, thrombin converts fibrinogen to fibrin

and activates platelets. It also activates coagulation factor XIII to crosslink fibrin and stabilize the thrombus. Finally, thrombin catalyzes its own generation via feedback activation of coagulation factors V and VIII [6]. Importantly, although thrombin is adsorbed to fibrin and bound to the newly formed clot, it retains most of its enzymatic activity and, thus, is able to locally stimulate further growth of the thrombus [7].

1.4 Basic treatment for ACS

The primary therapeutic goal in ACS is to disrupt the ongoing thrombotic process and, thus, to prevent progression from partial to complete and from intermittent to persistent coronary occlusion. These effects would be expected to translate into improved survival with fewer recurrent ischemic events. Antiplatelet therapy with aspirin has been proven to reduce the rates of mortality, MI and refractory angina after ACS [8, 9, 10, 11] and has become a basic component of drug therapy.

The pivotal role of thrombin in the pathophysiologic process makes it a natural target for drug therapy. Unfractionated heparin, an indirect thrombin inhibitor, has been shown to be superior to placebo [9, 12] and at least as effective as aspirin [13] in reducing the rates of mortality, MI and refractory angina. Furthermore, the combinations of aspirin with unfractionated heparin [14] and aspirin with low-molecular-weight (LMW) heparin, another indirect thrombin inhibitor [15], have been shown to be more effective than aspirin alone. However, even with a modern combination therapy including aspirin and heparin, in-hospital rates of both fatal or non-fatal MI and refractory angina necessitating urgent revascularization are in the range of 5–6% among patients with ACS [16]. This has prompted the investigation of more potent thrombin inhibitors such as hirudin.

1.5 Direct thrombin inhibition with hirudin

Hirudin is the most potent and specific thrombin inhibitor known to date [5, 17]. Natural hirudin is secreted in trace amounts by the salival glands of the medicinal leech (*Hirudo medicinalis*). It represents a family of highly homologous iso-polypeptides consisting of 65 or 66 amino acids. Hirudin binds directly to thrombin, forming a stoichiometric, slowly reversible complex with the enzyme [18]. The activity of hirudin is measured by means of a chromogenic [19, 20] or enzyme-linked immunosorbent assay [21]. One antithrombin unit is the amount of hirudin that neutralizes one unit of WHO preparation 89/588 of thrombin.

There are five mechanistic differences between hirudin and indirect thrombin inhibitors like heparin:

(1) Hirudin inhibits thrombin directly, i.e. independently of antithrombin III, whereas heparin does not.

(2) It binds almost exclusively to thrombin, whereas heparin binds non-specifically to acute phase proteins and to proteins secreted by activated platelets and endothelial cells.

(3) It is not inactivated by platelet factor 4, whereas heparin is [22].

(4) It markedly reduces growth of platelet-rich arterial thrombus on deeply injured artery and pre-existing mural thrombus [23], and even promotes dissolution of acute platelet thrombus [24] or mural thrombus [25], whereas heparin does not.

(5) Most importantly, it inhibits thrombin both in the fluid phase and when it is bound to fibrin [7] or fibrin degradation products [26], whereas heparin acts only on fluid-phase thrombin.

These findings form the pharmacological basis for the assumption that hirudin is superior to heparin at inhibiting thrombin activity and, thus, preventing thrombus formation and growth. Various experimental models of arterial injury and thrombosis have demonstrated that hirudin is a more effective antithrombotic agent than heparin [27, 28, 29, 30, 31]. Clinically, in patients with ACS, this is expected to translate into a reduced rate of CV death, new MI, or refractory angina necessitating urgent revascularization procedures.

1.6 Characteristics and clinical pharmacology of lepirudin

Lepirudin ([Leu^1,Thr^2]-63-desulfohirudin) is composed of 65 amino acids and has a molecular weight of 6,979.5 Dalton. It is distinguished from natural hirudin in that it has leucine instead of isoleucine as the first amino-terminal amino acid and is not sulfated at tyrosine 63. The specific activity of lepirudin is approximately 16,000 antithrombin units per mg.

The clinical pharmacology of lepirudin was described in the original NDA submission for HIT. No new clinical pharmacology data are included in the efficacy supplement. The studies described in the original submission dossier also formed the pharmacological basis for the investigation of lepirudin in the proposed new indication "acute coronary syndromes (unstable angina or acute MI without ST elevation)".